III. REMARKS

Claims Status

Claims 1-11 are pending. Claims 1-2, 4, 8, 10-11 have been amended; claims 3, 5-7 and 9 have been cancelled. Accordingly, claims 1-2, 4, 8 and 10-11 are currently under examination on the merits.

Priority

The examiner has not heretofore received English language translations of the priority documents. The translation is enclosed herewith, thus perfecting applicant's priority claim.

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2) but fails to comply with the requirements of 37 CFR 1.821 through 1.825 in that Table 2 of the instant application contain nucleic acid sequences which are not preceded by "SEQ ID NO:".

Applicants have amended Table 2 to recite the SEQ ID NOs of the listed oligos thereby obviating this ground for rejection.

Information Disclosure Statement

The listing of references in the Search Report and in the specification is not a proper information disclosure statement. Therefore, the references cited in the Search Report and in the specification have not been considered.

A revised invention disclosure statement is being submitted with the response.

Specification

The disclosure is objected to because of the following informalities:

1) The instant disclosure contains drawings, Figures 1-5; however, there is no brief description of the drawings in the specification.

Applicant has amended the specification to include the section "Brief Description of the Drawings" thus obviating this ground for rejection.

2) The abstract of the disclosure is objected to because it contains the word "said".

Applicant has amended the abstract thereby obviating this ground for rejection.

3) The instant disclosure contains Table 2 with nucleic acid sequences where the nucleic acid sequences are not preceded by SEQ ID NOs.

Applicant has amended the table to include the SEQ ID NOs. thus obviating this ground for rejection.

Claim Objections

Claims 2, 7, and 9 stand objected to for containing non-elected subject matter. Claim 2 has been amended; claims 7 and 9 have

been cancelled thus obviating this ground for objection.

***Claim Rejections - 35 USC § 112* second paragraph**

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention in that the claim does not recite the appropriate sequence id number.

Claim 1 has been amended to recite the appropriate SEQUENCE ID NUMBER the obviating this ground for rejection.

Claims 1-2 claim that the polynucleotide "specifically interacts with" the mRNA sequence. It is unclear to the examiner what is meant by the phrase "specifically interacts with", because neither the claims nor the specification describe what limitations are encompassed by the phrase.

Applicant has amended the claim to recite "binds" in place of "specifically interacts with", thus obviating this ground for rejection.

Further, with regard to claim 1, applicant has amended the claim to clarify that the claimed polynucleotide in the instant application is a polynucleotide hybridizing with either region of the hTERT sequence.

Claims 3 and 9 recite the limitation "the sequence region" in lines 1-2. These claims have been cancelled.

Claim 4 claims that the polynucleotide is "immobilized".

Applicant traverses this ground for rejection and reiterates the argument set forth in applicant's previous response. In addition, to add addition clarity, Applicant has amended claim 4 to indicate that the polynucleotide is immobilized on a specified carrier. It is common knowledge in the art regarding the techniques required to immobilize a polynucleotide on the specified carriers.

As recognized by the examiner, the specification discloses a number of different methods (e.g., crosslinking, binding to carrier, inclusion, adsorption, covalent binding, polyacrylamide resins, microencapsulation) on pages 8-9 of the specification. The breadth of the term "immobilization" described in the specification is broad because the method of immobilization is not crucial to the practice of the invention and any of the art recognized techniques may be utilized.

Claims 10-11 claim compositions comprising a polynucleotide and a "pharmaceutically tolerable carrier". Although the specification describes that "the pharmaceutical carrier may comprise additional materials and substances such as medical and/or pharmaceutical-technical adjuvants" (page 9), it remains vague and unclear to the examiner exactly what is encompassed by the term "pharmaceutically tolerable carrier" because the specification does not further elaborate on the claimed subject matter.

Applicant traverses this ground for rejection.

At the bottom of page 9 and the top of page 10 of applicant's specification applicant extensively characterizes what he means by pharmaceutically tolerable carrier, viz.

> "The invention also relates to a pharmaceutical composition comprising the poylnucleotides of the invention, optionally in combination with a pharmaceutically tolerable carrier. More specifically, the pharmaceutical carrier may comprise additional materials and substances such as medical and/or pharmaceutical-technical adjuvants. For example, medical adjuvants are materials used as ingredients in the production of pharmaceutical compositions. Pharmaceutical-technical adjuvants serve to suitably formulate the drug or pharmaceutical composition and, if required during the production process only, can even be removed thereafter, or they can be part of the pharmaceutical composition as pharmaceutically tolerable carriers. Formulation of the pharmaceutical composition is optionally effected in combination with a pharmaceutically tolerable diluent. For example, the diluents can be phosphate-buffered saline, water, emulsions such as oil/water emulsions, various types of detergents, sterile solutions, and the like. The pharmaceutical composition can be administered in association with a gene therapy, for example.

Applicant respectfully requests reconsideration of this ground for rejection.

35 U.S.C. 112: first paragraph, Enablement

Claim 10 stands rejected under 35 U.S.C. 112 as failing to comply with the enablement requirement in that the claim contains the preamble language, "pharmaceutical".

Per the examiner's suggestion, applicant has amended the claim to remove the superfluous word "pharmaceutical" thus obviating this ground for rejection.

Claims 3, 6, and 8 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in that to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus and the examiner argues that sufficient disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof of any and all modifications and mutations as claimed in claims 3 and 8, and that of claim 6 embraces any and all molecules that support transport to the target site.

With regard to chemical modifications, the examiner states that the specification discloses the phosphorothioate modification, incorporation of ribonucleotides and partial terminal modification (page 6) but is silent about any hTERT antisense oligonucleotide that is chemically modified.

With regard to mutations, the examiner states that although the specification recites the different types of mutations as claimed claim 3 (page 3), it does not disclose any antisense oligonucleotide possessing any of the claimed mutations. The claimed subject matter "another molecule" in claim 6 reads broadly on anything that supports transport, uptake, and distribution of the polynucleotide to a target cell, but the specification does not set forth any species of such molecule

nor does it adequately describe what is meant by "another molecule".

The examiner concludes that as broadly claimed, the specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed in claims 3, 6, and 8, especially because it does not describe any species of hTERT antisense oligonucleotide that contains mutations (claim 3) or complexed with another molecule (claim 6) or is chemically modified (claim 8).

Applicant traverses this ground for rejection.

Claims 3 and 6 have been cancelled; claim 8 has been amended to limit the modification to phosphothioate bonds thus obviating this ground for rejection.

Claim Rejections - 35 USC § 102(b)

Claims 1, 3-9 and 11 stand rejected under 35 U.S.C. 102(b) as being anticipated by Monia et al. (US 2002/0045588 Al).

The claims were previously drawn to a polynucleotide that specifically interacts with the sequence 2176-2250 or 2296-2393 of SEQ ID NO:18, wherein the polynucleotide contains mutations, immobilized (the polynucleotide is fixed on specific carriers), the polynucleotide is antisense oligonucleotide, complexed with a molecule that supports cellular uptake, modified with phosphorothioate bonds, and a kit comprising the polynucleotide and a pharmaceutical carrier.

The examiner states that Monia et al. teach anti-hTERT

oligonucleotides that hybridize with the hTERT mRNA sequence. They teach SEQ ID NO:12 whose 10 consecutive nucleotides "CCAGGGCACG" align with the region of 2308-2318 of SEQ ID NO:18 ("CCATGGGCACG"), wherein the nucleotide "T" is inserted in the instant case.

Applicant has amended claim 1 which is now limited to a polypeptide which is an antisense oligonucleotide and complementary to the selected target regions (according to former claims 7 and 9) wherein the target region is selected from region 2206-2225 (SEQ ID NO 4) and/or 2331-2350 (SEQ ID NO 8) of the human telomerase according to former claim 2 with accession number AF015950 (SEQ ID NO 18).

Former claims 3, 5-7 and 9 have been cancelled. Claim 2 has been amended. Claim 2 as amended now claims the antisense oligosequences set forth in Table 2, SEQ ID NO: 10 (ASteI2206-2225) and SEQ ID NO: 13 (AStel2331-2350).

As already mentioned, a single polynucleotide of the invention can hybridize either with a target of the first region or the second region. That follows inevitably from the nature of the polynucleotide which sequence determines its binding capability to a single complementary sequence target.

The oligo sequences of the invention are disclosed in Table 2. The oligos for the selected target regions are presented with AStel2206-2225 which is SEQ ID NO. 10 in the sequence listing and ASteI2331-2350 which is SEQ ID NO.13 in the sequence listing.

Former claims 4, 8, 10 and 11 have been amended following

Examiner's objections.

The amended claim set is novel over the cited document of Monia et al. The claims refer to the two (2) selected antisense oligonucleotides which specifically interact (bind) to the target sequences of SEQ ID NO 4 and/or 8 which are the target regions 2206-2225 and 2331-2350 and which do not overlap with the region 2308-2318 cited by Monia et at.

As already mentioned the antisense oligonucleotides of the present application affect a reduction in viability of more than 65% (cf. Example 1). Furthermore, the oligos cause a synergistic booster effect if simultaneously administered with chemotherapeutics (cf. Example 2).

The inventors have previously prepared a paper manuscript further pointing out the unexpected benefits which was previously submitted with the response filed June 1, 2006 and which is again enclosed for convenience.

As is disclosed at column 2 on page 1, the aim of the presented study was to characterize genome-wider expression profiles of the BCa cell line EJ28 after transfection with 2 hTERT ASODNs [namely with the selected oligos ASt2206 (SEQ ID NO. 10) and ASt2331 (SEQ ID NO. 13) as the molecular basis of their growth suppressing function.

After multiple cycles of an instillation therapy (based on an anti-hTERT-AS-ODN transfection followed by chemotherapy at the next day, two times per week, over a period of 2 to 3 weeks) against orthotopically superficial human bladder cancer cells (cell line EJ28), a significantly reduced tumor growth compared

to the control treatment (only chemotherapy) was found in a mouse model. Dramatically smaller tumor volumes or an absence of tumor formation was determined for several mice of the combinational treatment group (AS-ODN + chemotherapy).

Surprisingly, a relatively large amount of the tumor tissue was not viable (netrotic areas) in those treated animals with detectable tumor masses. These inhibition effects were exclusively observed for the treatment group consisting of anti-hTERT AS-ODN. Moreover, detailed histological examinations indicated a massive induction of apoptosis as well as significant local inflammation. The exact mechanisms of this therapeutic efficacy are unknown so far for the *in vivo* model, however, the observed enhancing effect of the AS-ODN-therapy is a significant feature of the AS-ODN constructs. This implies a heterogeneous, complex and significantly anti-proliferate efficiency of these molecules against human bladder tumors.

As can be seen from column 1 on page 3 (F3 paragraph), the 2 hTERT AS-ODNs caused total numbers of changed genes of 59 (ASteI2206) and 101 (ASte12331), respectively, whereby most of them were upregulated (Fig. 3a).

At column 2 of page 3 (F4 paragraph), the inventive 2 hTERT AS-ODNs are shown to have efficiently reduced the numbers of EJ28 cells within the first 24 hr after transfection in comparison to the NS-ODN (Fig, 4).

Claims 1-2, 7, and 9 stand rejected under 35 U.S.C. 102(e) as being anticipated by Bentwich (US 2006/0257851).

As applicant's priority date is earlier than that of the

reference, this rejection is obviated.

A translation of the foreign priority papers has been filed herewith. The certification has not yet arrived so the translations are being submitted herewith as a convenience to the examiner. The certifications will be submitted as soon as received.

The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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